REMARKS

I. Claim Status

Applicants have amended claims 1, 3, and 11; added new claims 31-32, which read on the elected invention; and cancelled claims 25-27. Upon entry of these claims, claims 1, 3, 5, 6, 11, 12, 23, 24, and 28-32 will be pending. All amendments are without prejudice.

Support for these amendments can be found throughout the application, including paragraphs 43, 89, 143, and Table 3 (paragraph 152) of the published application, U.S. Patent Application Publication No. 2006/0292129 A1. Entry of this amendment is courteously solicited.

II. Withdrawn rejection

Applicants acknowledge, with thanks, the Examiner's withdrawal of the previous rejection under 35 U.S.C. §102(b) over Ichiyama *Kari Igaku Kenkyusho Zasshi, JP* 51(3-4): 93-110 (2000) ("Ichiyama") as evidenced by Benoist *et al.Immunol. Let.* 43(1):45-55 (1992) ("Benoist ") and Karsten *et al. Cancer Res.* 58: 2541-49 (1998) ("Karsten"). The Examiner acknowledges that "Ichiyama M does not describe a cell line which expresses TF, MUC1 and glycophorin wherein TF is exposed as reflected by binding of specific antibodies." Office Action at 3.

III. Maintained rejection under 35 U.S.C. §103(a)

A. The rejection

Claims 1, 5, 6, 11, 12, 23, and 24 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Ichiyama as evidenced by Hinoda *et al. J. Clin. Lab. Anal.* 7(2): 100-04 (1993, Abstract) ("Hinoda"), in view of Benoist, and Karsten and further in view of U.S. Patent No. 7,268,120 to Horton *et al.* ("Horton") and Springer *J. Mol. Med.* 75: 594-602 (1997) ("Springer"). Specifically, Ichiyama is cited as describing the cell line K562 cotransfected with tumor-associated epithelial human mucin MUC1 cDNA and with human B7 cDNA and Benoist

is cited as evidence that "K562 tumor cells present glycophorin A (GPA) on the cell surface." Office Action at 4. The Office acknowledges that the combined disclosure of Ichiyama and Benoist fails to teach the presence of TF in the cell line K562, and relies on Karsten's description of synthetic MUC1-derived peptide sequences engineered to contain the Core 1 epitope to remedy this defect. *Id.*

The Office further acknowledges that the combined disclosure of Ichiyama, Benoist and Karsten "fails to teach that enzymatic removal of the sialic acid covering the T[F] antigen disaccharide in glycophorin to obtain asialoglycophorin..." Office Action at 5. To allegedly remedy this deficiency, the Office cites to Springer for a description of "crude preparations of enzymatically desialylated glycophorin from O RBC carrying high densities of TF...." *Id.* Finally, the Office cites to Horton to evidence that it was allegedly routine in the art to use ex vivo polynucleotide constructs and selective transfection of malignant cells containing polynucleotides expressing therapeutic or prophylactic molecules. *Id.*

To facilitate prosecution, Applicants amended the claims on May 25, 2010 to include the clarification "wherein the TF is exposed," which the Office previously indicated would free the claims of the art. The Examiner now states that

> Applicants have not submitted new arguments to rebut rejection of claims 1, 5, 6, 11, 12, 23, 24, 26, and 28 under 35 USC § 103 which was previously maintained in the Office Actions filed on 01-14-2010 and 02-25-2010[1]. Of note Figure 1 in the specification evidences that wild type K562 cells before magnetic separation express TF, Tn, GPA, AGPA and MUC1 markers. What [A]pplicants have obtained with enzymatic desialylation with neuramidase treatment is an enriched population K562-derived cell for TF, i.e., NM-F9 and NM-D4. Therefore, claims 1, 5, 6, 11, 12, 23, 24, 26, and 28 remain rejected under 35 USC 103 for the reasons already of record and the reasons set forth in the paragraph above.

Office Action at 7. Applicants disagree.

[1] Applicants note that the "Office Action" mailed February 25, 2010 was merely a Panel Decision from Pre-Appeal Brief Review that presented no substantive grounds of rejection. The Advisory Action of January 14, 2010, in turn, simply ignored Applicants' arguments of record, which were summarized in the Pre-Appeal Brief Request for Review, filed December 23, 2009.

B. Applicants' response

The Office continues to rely on incomplete analysis of the cited art and the teachings of the present application. For example, Karsten is limited to studies of ***synthetic glycopeptides*** made by ***cell-free*** solid phase chemical synthesis and gives no motivation to modify the cell line of Ichiyama. Springer describes treating red blood cells with ***exogenous enzymes*** in order to display antigens and gives no motivation to modify the cell line of Ichiyama to produce a cell line that makes and displays antigens ***without exogenous enzymes***—*i.e.*, a cells line that ***synthesizes and expresses*** TF, MUC1, and GPA. The application, in turn, describes many of the advantages of the claimed cell line that can, without exogenous enzymatic treatment, make and display these antigens on the cell surface. These issues are addressed in turn.

1. Karsten is limited to cell-free studies of synthetic glycopeptides and gives no basis to modify any *cell line*

Karsten describes ***synthetic*** MUC1-derived peptides made by multiple-column solid-phase chemical synthesis and ***engineered*** to contain TF and Tn, to test antibodies. *See* Karsten at page 2541, second paragraph of Materials and Methods. **Karsten's *cell-free* studies simply have *no relevance* to the cell line of Ichiyama, let alone the claimed cell line.**

To the extent that the Office may be arguing that Karsten's methods of chemical synthesis of glycopeptides could be applied to the cells of Ichiyama to make TF *in situ* on the cell surface, this argument must fail for two reasons. ***First***, there is no basis in any of the cited references that would lead the skilled artisan to believe Karsten's methods even *could* be applied to live cells. Indeed, the harsh chemical synthesis described in Karsten makes this highly unlikely. ***Second***, even if Karsten's methods could be applied to the cells of Ichiyama—and Applicants submit that they can not and moreover there is no motivation to do so—the result, at most, would be a cell line that simply has TF on its surface ***and not the claimed cell line that makes TF***—*i.e.*, that synthesizes and expresses it. Thus, Karsten does not support the rejection.

2. *Springer* requires exogenous enzymatic treatment to display antigens—the claimed cell lines do not

Springer's report of crude RBC preparations enzymatically treated to display AGPA does not support the present rejection, either. Again, this is at least because ***the claimed cell line needs no exogenous enzymatic treatment to display TF, MUC1, and GPA on the cell surface***, *i.e.*, the cell line ***synthesizes and expresses*** them. The Office's confusion on this point appears to stem from experiments described in the application where the NM-F9 and NM-D4 cell lines were subjected to neuraminidase treatment. *See, e.g.*, Figure 2 and Table 2, as well as the discussion in, *e.g.*, paragraphs 127, 131 and 132 of the published application. ***This data, however, shows that Applicants' cell lines make high levels of TF without exogenous neuraminidase treatment.*** Only a slight increase in TF was observed in NM-F9 after neuraminidase treatment—while ***K562 cells are "negative and can only reach a TF level comparable to NM-F9 after neuraminidase treatment."*** Paragraph 132 of the published application, emphasis added.

Therefore Springer does not support the rejection.

3. The Office has not considered the advantages of the claimed cell lines over those proffered in the rejection

The Office's reliance on Springer in the rejection ignores the recited claim feature that the cell line synthesizes and express TF, MUC1, and GPA; as well as the advantages of such a cell line, some of which are discussed in the application:

> The present invention uses these large advantage of AGPA in [the] form of a cell line that stably express AGPA. ***This has a lot of advantages compared with the conventional preparation of AGPA from blood cells***. For example
> 1) ***there is no need of any enzymatic treatment*** for the production of AGPA since the cell lines presented in this invention synthesize the TF-positive AGPA in contrast to red blood cells which synthesize the TF-negative GPA.
> 2) ***It does not need preparation from blood samples which can be contaminated with viruses and prions and which are heterogeneous*** in composition, highly variable from batch to batch and a difficult purification process based on phenol extraction.

Paragraph 15 of the published application, specifically referencing Springer, emphasis added.

Accordingly, the cell lines recited in the previous claims ***have numerous advantages over,*** and are not obvious over the combined teachings of Ichiyama, Hinoda, Benoist, Karsten, Horton, and Springer.

4. The amended claims are further distinguished over the art and the claimed cell lines have unexpected advantages

To facilitate prosecution, Applicants have amended the claims to include the feature "wherein the cell line is capable of inducing a humoral immune response against the TF antigen." There is no teaching, suggestion, motivation, or other basis in the combined teachings of Ichiyama, Hinoda, Benoist, Karsten, Horton, and Springer that would lead the skilled artisan to a cell line that synthesizes and expresses on the cell surface TF antigen, MUC1, and glycophorin, wherein the cell line is capable of inducing a humoral immune response against the TF antigen—let alone with the necessary reasonable expectation of success.

Furthermore, as previously noted, cell lines provided by the invention were shown, surprisingly, to be capable of inducing a desirable IgG response *in vivo* in NMRI and NOD/SCID mice. *See* Table 3 and paragraph 56 of the published application ("[t]he induction of an IgG response indicates a switch of antibody class associated with a T helper cell immune response as well as induction of memory immune responses against the above antigens including the carbohydrate antigens."). These significant results further rebut any *prima facie* allegation of obviousness.

Applicants ask that the rejection be withdrawn.

IV. Objection to the specification

Applicants have amended the paragraphs corresponding to paragraphs [0023] and [0039] of the published application to remove web addresses, as requested by the Examiner, rendering the objection moot.

V. Rejection under 35 U.S.C. §112, second paragraph

Claims 1, 3, 5, 6, 11, 12, and 23-30 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite due to the term "wherein the TF is exposed." Office Action at 8.

Without acquiescence to the Examiner's position, the claims have been amended to delete the term "wherein the TF is exposed," rendering the rejection moot.

VI. Rejection under 35 U.S.C. §112, first paragraph: written description

Claims 25-27 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description support. According to the Office, the terms "wherein the cell line is obtained [sic] from a TF-negative cell line" (claim 25) and "wherein the cell line is obtainable from an immortalized cell line" (claim 26) are not adequately supported by the application. Claim 27 is included in the rejection, presumably due to its dependence on claim 26, although no specific reasons are given.

Without acquiescence, claims 25-27 have been deleted, rending the rejection moot.

VII. New rejection under 35 U.S.C. §103(a)

Claims 1, 28, and 29 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over Ichiyama, Hinoda, Benoist, Karsten, Horton, and Springer, as summarized under heading III, *supra*, and further in view of Suzuki *et al. Mutat. Res.* 395: 75-82 (1997, abstract) ("Suzuki"). Office Action at 12. Suzuki was cited by the Office to show that "mutagenic agents such as ethyl methane sulfonate (EMS) are used for induction of gene mutations and chromosomal aberrations at the O6 position of guanine (abstract)." *Id.*

Applicants traverse. Suzuki does not remedy the deficiencies of Ichiyama, Hinoda, Benoist, Karsten, Horton, and Springer described above. The combination of these references does not teach or fairly suggest a cell line which synthesizes and expresses on the cell surface Thomsen-Friedenreich antigen (TF), mucin 1 (MUC1), and glycophorin, wherein the cell line is capable of inducing a humoral immune response against the TF antigen, let alone the advantages of such a cell line. Accordingly, this rejection should be withdrawn.

VIII. Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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